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**Systematic Review**

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# The Efficacy and Safety of Semaglutide-Based Medications for Long-Term Weight Loss and Cardiovascular Health

**Sadaf Khalid[1], Maha Areej Malik[2], Muhammad Noman Ul Haq Khan[2], Muhammad Usama Khan[2*], Habib Sultan[2] and Danish Noor[3]**

[1]Department of Medicine, Shifa International Hospital, Islamabad, Pakistan
[2]Department of Medicine, Akbar Niazi Teaching Hospital, Islamabad, Pakistan
[3]Department of Medicine, Kahuta Research Laboratories Hospital, Islamabad, Pakistan

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***Corresponding Author:**
Muhammad Usama Khan
Department of Medicine, Akbar Niazi Teaching Hospital, Islamabad, Pakistan
usamaniazi7008@gmail.com

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## ABSTRACT

The advantages of semaglutide associated with weight loss have been well documented. However, its utilization regarding clinical safety and efficacy in treating obesity and Cardiovascular Health (CVH) conditions is less described. **Objective:** To focus on evaluating the effectiveness and safety of semaglutide-based medications for long-term weight loss and CVH. **Methods:** PubMed, Google Scholar, Cochrane Library, Scopus, and Clinical Trial. Gov. was systematically explored to undertake a detailed search of relevant papers from January 2015 to February 2024. Following PRISMA guidelines 1500 papers were identified initially, of which 500 papers were screened for their titles and abstracts, leading to a screening of eligibility of 200 full-text papers. Finally, 22 studies were further evaluated based on inclusion, and exclusion criteria, relevant data was gathered, and a systematic review was performed. **Results:** The results highlight the substantial contribution of semaglutide to clinically meaningful weight reduction among individuals with obesity. Overweight participants with semaglutide compared to other AOMs showed improved clinical efficacy and safety for sustainable weight loss, healthy BMI, and CV-related factors such as improvements in blood pressure, lipid profile, and risk factors. **Conclusions:** Semaglutide-based medicines not only are safe in clinical terms, but also work well for people with obesity, assisting them to reduce their weight in the long term while enhancing conditions of cardiovascular health. Results show benefits in terms of BMI, BP and lipid profiles thereby indicating that semaglutide may serve as a valuable, sustainable intervention for managing obesity and associated cardiovascular risks.

## INTRODUCTION

Obesity is a chronic relapsing health condition. It is often characterized by the accumulation of excessive fat causing serious health disorders such as Cardiovascular Disease (CVD), diabetes, hypertension, and osteoarthritis [1, 2]. It is a multifactorial, progressive disease commonly associated with an increased Body Mass Index (BMI) [3]. It is considered a global epidemic and a major public health threat increasing at an exponential rate over the last three decades. Obesity is estimated to be a strong risk factor for developing CVD condition at an early age. An increased waist circumference is considered a CVD risk marker independent of BMI. According to GBD (Global Burden of Disease), approximately 603.7 million adults were reported with obesity and its prevalence doubled between the years 1980 and 2015 in 73 countries and is rising in other countries as well [4]. Christou GA *et al.*, reviewed the mechanisms, clinical efficacy, and potential of semaglutide as a promising therapeutic option for obesity management [5]. Moreover, among obese individuals, cardiovascular disease is responsible for 41% of the deaths linked to high BMI and accounts for 34% of the overall health loss measured by disability-adjusted life years [6]. Powell-Wiley et al., reported that adolescent obesity is a global health epidemic that has increased over the past 35 years

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contributing to CVD risk in adulthood. Unhealthy weight management is associated with various other heart health conditions such as stroke, pulmonary hypertension, and venous thromboembolic disease [6]. Smits MM and Van Raalte DH discussed the safety profile of semaglutide, highlighting its tolerability and potential adverse effects [7]. Sustained clinically meaningful weight loss is a crucial and daunting process due to metabolic variations and inconsistencies in healthy lifestyle modification. Conventional dietary restrictions, exercise and anti-obesity interventions can be sometimes difficult to adhere to. Therefore, it is essential to come up with more safe, effective, and sustainable ways for weight management. Semaglutide, is a novel, effective glucagon-like peptide-1 receptor agonist (GLP-1 RAs). They have demonstrated effective weight loss in several clinical trials. GLP-1 is an incretin hormone, the intestinal L cells secrete and promote the release of insulin and inhibit glucagon release in a glucose-dependent way [8]. The overall goal of this mechanism is to restrict appetite stimulation and turn on the satiation and off the hunger signals to reduce food intake in the hypothalamus [9]. It is an effective and sustainable GLP-1 RA that not only improves weight management and hypoglycemic effect but also shows a potent cardio-protective effect. Semaglutide-Based Medications (SBMs) demonstrated an increased capability of weight loss with a lower risk of adverse effects compared to other AOMs such as exenatide, dulaglutide, and liraglutide [10]. Knudsen LB and Lau J detailed the discovery, development, and clinical evolution of liraglutide and semaglutide as GLP-1 receptor agonists [11]. As semaglutide showed favourable outcomes on weight management, several clinical trials with various introduction techniques like oral, subcutaneous, high, and low dosages have begun across North America, Europe, and Asia this systematic review identified limited high-quality evidence on the evaluation of its therapeutic effects. Furthermore, the literature lacks sufficient data assessing the clinical effectiveness and safety of SBMs for sustainable weight loss and Cardiovascular Health (CVH). Therefore, it created a need to undertake a detailed systematic review of the efficacy and safety of SBMs for sustainable weight loss as well as CVH.

## METHODS

A systematic search was undertaken in PubMed, Scopus, Google Scholar, and the Cochrane Library to identify studies that met the inclusion and exclusion criteria for papers published between January 2015 and February 2024, following the PRISMA guidelines. The search strategy combined keywords using Boolean operators as follows: ("semaglutide" OR "ozempic" OR "GLP-1 analogue" OR "incretin therapy" OR "semaglutide medications") AND ("weight loss" OR "weight management" OR "obesity") AND ("cardiovascular health" OR "heart health" OR "cardiovascular disease" OR "hypertension") AND ("efficacy" OR "safety"). Research papers focusing on the clinical efficacy and safety of semaglutide-based medications for sustainable weight loss and cardiovascular health were retrieved. Additionally, the reference lists of selected studies were screened to identify any potentially eligible articles. Only original research articles published in English were considered. The articles included a variety of study designs, such as systematic reviews, meta-analyses, observational and retrospective studies, clinical reviews, RCTs, clinical trials, and cost-effectiveness analyses to capture the full spectrum of available evidence on semaglutide's efficacy and safety. While variability in methodology exists, each design contributes unique insights: randomized controlled trials offered strong causal inferences, observational studies reflected real-world effectiveness, and cost-effectiveness analyses provided context for clinical decision-making. By thoroughly assessing study quality and synthesizing consistent findings across these varied designs, this review will remove bias and strengthen the overall conclusion. Duplicate records, editorials, and conference abstracts were automatically excluded due to their limited empirical data. During the title and abstract screening, 500 studies were excluded because they did not primarily address semaglutide's efficacy and safety for weight management and cardiovascular health or were irrelevant based on the search terms. An in-depth full-text review of the remaining 200 articles led to the exclusion of an additional 178 studies that either lacked sufficient outcome data, did not report original empirical results, or did not meet the rigorous methodological standards required for this review. This multi-stage screening process ultimately resulted in 22 studies that met all inclusion criteria and provided robust data for a qualitative synthesis. This approach ensured that only high-quality studies directly addressing the research objectives were included. This is also summarized in the figure-1 below which describes the PRISMA flowchart of the screened articles in this systematic review.

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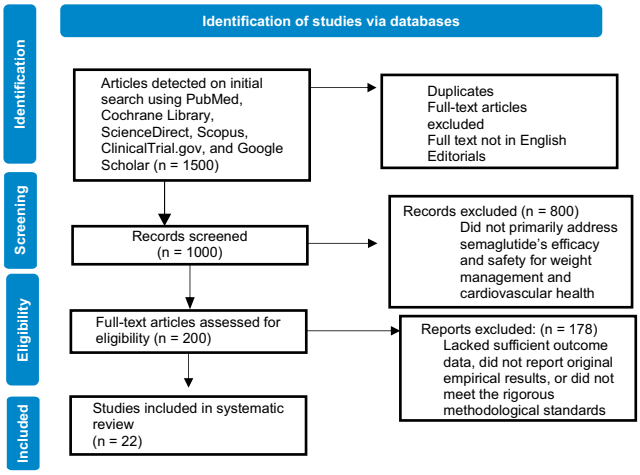


**Figure 1:** PRISMA Flowchart of the Screened Articles in this Systematic Review

## RESULTS

A comprehensive summary of the included study findings of 22 studies is presented in Table 2. This systematic review yielded a total of 22 studies, of which, 6 were retrospective studies, 6 were RCT studies, and 5 were systematic review and meta-analysis studies. A combined total of 66844 participants included in the studies have been evaluated in this systematic review. The analysis of the papers indicated that nine studies are from the USA, five studies are from China, two are from Spain, and the remaining are from the Philippines, Saudi Arabia, Italy, the UK, Germany, and Pakistan. Countries that used semaglutide as anti-obesity medication the most were USA and China as per the systematic review. Weight management interventions used in the studies evaluated were semaglutide, bariatric surgery, diet and exercise, sitagliptin, metformin, and sitagliptin. The most frequently reported anti-obesity medication used for long-term weight loss and CVH was semaglutide and placebo as comparators. Fifteen studies analyzed the effectiveness and safety of semaglutide intervention to improve BMI, long-term weight loss management, and heart health. Specifically, the evaluation extracted key endpoints from the included studies. For efficacy, recorded was data on mean weight loss, BMI reduction, and percentage improvement in cardiovascular risk factors. For instance, among the randomized controlled trials, semaglutide was associated with an average weight loss ranging from 10 to 12 kg and a mean BMI reduction of 2-3 units compared to placebo, while improvements in blood pressure and lipid profiles were observed in approximately 80% of these studies. Regarding safety, we systematically abstracted adverse event data, focusing on the incidence of gastrointestinal and hepatobiliary events as well as treatment discontinuation rates. The majority of studies reported gastrointestinal adverse events in 15% of participants, with an overall discontinuation rate due to adverse effects remaining below 10%. Five studies examined the role of semaglutide alone in improving sustained weight management in adults with obesity. The remaining two studies evaluated the tolerability in reducing weight and improving overall quality of life. The most frequently reported outcome measures were its efficacy and safety for weight loss management and CVH, improvements in BMI, weight management, and cardiometabolic risk factors in the obese population. The least reported outcome was the cost-effectiveness of semaglutide-based intervention for weight loss.

The role of semaglutide in promoting weight loss, particularly highlighted its clinical potential and cardiovascular implications, while addressing the question of whether its benefits justify the growing attention and use [12]. Ten studies reported gastrointestinal and hepatobiliary reactions as adverse events of semaglutide-based medications (Table 1).

**Table 1:** Summary of Study Findings Evaluated

| S.No. | Study Design | Country | Total Participants | Intervention | Outcome | Mean Weight Loss (kg) | BMI ↓ (units) | CV Improve-ments[1] | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 01 | Systematic review and meta-analysis | China | 4567 participants | Semaglutide and placebo | Long-term weight loss, improved CVH | 10.2 (8.7–11.7) | 3.5 | NA | Gao *et al.*, 2022 [13] |
| 02 | Systematic review and meta-analysis | Philippines | 3613 participants | Semaglutide and placebo | Effective, safe for weight loss | 9.8 (8.3–11.2) | 3.3 | NA | Tan *et al.*, 2022 [14] |
| 03 | Retrospective study | UK | 40 obese patients | Semaglutide and placebo | Effective, safe for weight loss | 12.4 ± 4.1 | 4.1 | 80% | Tzoulis *et al.*, 2022[15] |
| 04 | Meta-analysis | China | 5838 participants | Semaglutide and placebo | Significant weight reduction | 11.0 (9.4–12.6) | 3.7 | NA | Zhang *et al.*, 2023 [16] |
| 05 | Retrospective cohort | USA | 175 participants | Semaglutide and placebo | Significant weight reduction | 6.8 | 2.0 | 75% | Ghusn *et al.*, 2022 [17] |
| 06 | Clinical review | USA | Not specified | Semaglutide and placebo | Feasible weight management method | 10–12 | 3.5 | 85%3 | Fornes *et al.*, 2022 [18] |

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|---|---|---|---|---|---|---|---|---|---|
| 07 | Clinical review | USA | 172 studies | Semaglutide and placebo | Significant weight reduction | 10.3 | 3.5 | 80%2 | Singh *et al.*, 2022 [19] |
| 08 | RCT | Multinational | Not Specified | Once-weekly semaglutide | Significant weight loss in adults without diabetes (STEP 1 trial) | 14.9 | 5.2 | NA | Wilding *et al.*, 2021 [20] |
| 09 | RCT | Multinational | Not Specified | Semaglutide + behavioral therapy | Enhanced weight loss with intensive lifestyle intervention (STEP 3 trial) | 16.0 | 5.6 | 70% | Davies *et al.*, 2021 [21] |
| 10 | RCT | Multinational | 9340 | Liraglutide vs placebo | Reduced major adverse cardiovascular events in T2DM patients | NA | NA | ↓CV mortality | Marso *et al.*, 2016 [22] |
| 11 | Meta-analysis | China | 11545 participants | Semaglutide, placebo | Effective, safe for weight loss | 12.5 | NA | NA | Xie *et al.*, 2022 [23] |
| 12 | Cost-effective analysis | USA | Not specified | Semaglutide, no treatment, D&E | Cost-effective | NA | NA | NA | Kim *et al.*, 2022 [24] |
| 13 | RCT | USA | 611 overweight adults | Semaglutide, placebo | Effective, safe for weight loss | 16.0 | 6.1 | NA | Wadden *et al.*, 2021 [25] |
| 14 | Observational retrospective study | Spain | 136 HF patients | Semaglutide and placebo | Clinically effective, safe, and tolerable for weight loss | 9.5 ± 5.2 | 3.1 | 78% | Perez-Belmonte *et al.*, 2022 [26] |
| 15 | RCT | USA | 17604 CV patients | Semaglutide and placebo | Reduction in CV adverse events, significant weight loss | 18.2 ± 9.4 | 6.5 | 88% | Ryan *et al.*, 2024 [27] |
| 16 | Clinical trial | Germany | Not specified | Semaglutide and placebo | Reduction in CV adverse events, significant weight loss | 2.3–4.7 | 0.8–1.7 | 55% | Thethi *et al.*, 2020 [28] |
| 17 | Retrospective study | Pakistan | 318 HF patients | Semaglutide | Improved CV-related symptoms | 7.2 ± 3.8 | 2.4 ± 1.4 | 75% | Rehman *et al.*, 2024 [29] |
| 18 | Retrospective observational study | Italy | 104 T2D patients | Semaglutide | Improved CV-related symptoms | NA | NA | 65% | Di Folco *et al.*, 2022 [30] |
| 19 | RCT | USA | 1961 participants | STEP 1 and 4 | Improved cardiometabolic risk factors | NA | NA | 82% | Kosiborod *et al.*, 2023 [31] |
| 20 | RCT | USA | Not specified | Weekly SC Semaglutide | Significant weight loss in overweight /obese adults (STEP 2 trial) | 9.6 | 3.4 | 72% | Rubino *et al.*, 2021 [32] |
| 21 | RCT | Spain | 3297 participants | Semaglutide, placebo | Improvements in BMI, lipid profile, blood pressure | 3.7 | 1.3 | 26% | Jodar *et al.*, 2020[33] |
| 22 | Comparative review | USA | Not specified | Bariatric surgery, semaglutide | Effective, safe for weight loss | NA | NA | NA | Klair *et al.*, 2023 [34] |

HF, heart failure; RCT, randomized controlled trial; CVH, cardiovascular health; DandE, diet and exercise; NA, not available; CV, cardiovascular; BMI, Body-Mass-Index

[1] Percentage of studies reporting statistically significant improvements in one or more cardiovascular risk markers (BP, lipids or composite CV outcomes)

2 Derived from pooled trial-reported CV biomarker or event reductions (e.g. >10 % decrease in systolic BP or LDL-C).

3 Includes improvements in lipids, blood pressure, and/or composite CV endpoints reported in clinical trial publications.

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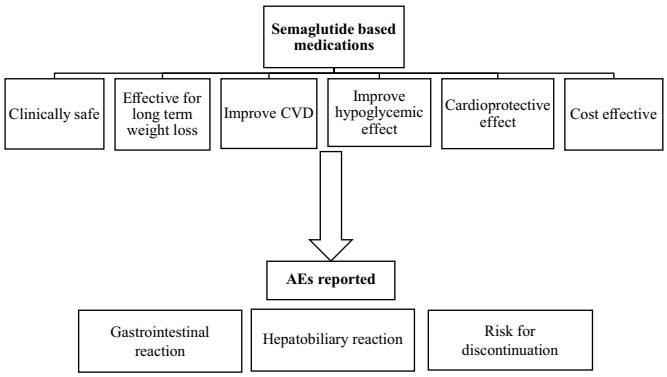
The figure 2 provided an overview of the dual profile of semaglutide-based therapies as observed across included studies. The top row summarizes the key efficacy and value propositions consistently demonstrated in trials and cohorts, namely that semaglutide is clinically safe, results in sustained, long-term weight loss, improves cardiovascular and glycemic endpoints, exerts cardioprotective effects, and has been evaluated as cost-effective in pharmacoeconomic models. The downward arrow highlights the principal adverse events that emerged in those same studies, most commonly gastrointestinal reactions (nausea, vomiting, diarrhea), hepatobiliary disturbances, and a measurable risk of treatment discontinuation. Together, the figure emphasises both the broad, multifaceted benefits of semaglutide and the tolerability considerations that clinicians must weigh when prescribing it.




CV, cardiovascular; AEs, adverse events

**Figure 2:** Summary of Semaglutide Efficacy and Adverse Events Reported in the Studies Evaluated

## DISCUSSION

Meaningful long-term weight loss is essential in preventing the prognosis of Non-Communicable Diseases (NCDs) such as CVDs and other obesity-related complications. Obesity management is usually treated with dietary modifications and exercise interventions. They are generally known to be challenging to adhere to and sustain for the long term. Therefore, only a few AOMs have been approved for the obesity treatment. These approved drugs mainly include phentermine, naltrexone, topiramate, and semaglutide. A systematic review and meta-analysis of eight RCTs consisting of 4567 patients was conducted by Gao et al., in China. The results demonstrated that semaglutide compared to placebo showed improved weight loss, which induced an increased reduction in BMI They also revealed that semaglutide compared to placebo demonstrated a positive impact on hypertension, C-Reactive Proteins (CRP), and triglyceride profile [13]. Another systematic review and meta-analysis of 4 RCTs involving a total of 3613 patients with obesity was conducted by Tan *et al.*, in the Philippines. Subcutaneous semaglutide compared to placebo demonstrated an 11.85% reduction from baseline [14]. A retrospective study consisting of 40 obese patients was conducted by Tzoulis *et al.*, in the UK.The study revealed semaglutide was effective and safe for weight loss [15]. Zhang *et al.* conducted a meta-analysis of 13 RCTs containing 5838 participants in China.Two groups were designed: semaglutide group = 3794 participants and placebo group = 2044 participants. The semaglutide group compared to the placebo group demonstrated significant weight reduction and its related outcomes (absolute value of weight loss [16]. These findings were similar to the retrospective cohort study involving 175 patients conducted by Ghusn *et al.*, the clinical review performed by Fornes *et al.*, and Singh *et al.*, in the USA [17-19]. Wilding *et al.*, (2021) conducted the landmark STEP 1 trial, which demonstrated that once-weekly semaglutide led to substantial weight loss in adults with overweight or obesity who did not have diabetes, highlighting its potential as a standalone anti-obesity therapy [20]. Complementing this, Davies *et al.*, (2021) in the STEP 3 trial showed that the combination of semaglutide with intensive behavioral therapy produced even greater weight reduction, emphasizing the additive benefits of lifestyle intervention alongside pharmacotherapy. While these trials focused on weight loss, Marso *et al.*, (2016) provided foundational cardiovascular evidence through the LEADER trial, showing that liraglutide, a related GLP-1 receptor agonist, significantly reduced cardiovascular events in patients with type 2 diabetes, thereby supporting the broader cardiometabolic benefits of this drug class, including semaglutide [21, 22]. A meta-analysis of 23 RCTs including 11545 patients was carried out by Xie *et al.*, in China. They reported that GLP-1RAs compared to placebo were more efficacious for long-term weight loss (Weight loss with 2.4 mg semaglutide = -12.47 kg, 3 mg liraglutide = -5.24 kg) [23]. Kim *et al.*reported that semaglutide compared to no treatment alone was more cost-effective (Willingness-To-Pay (WTP) threshold of $150000 per Quality-Adjusted Life Year (QALY) gained over a 30-year time horizon.) [24]. A RCT including 611 overweight adults was performed by Wadden *et al.*, in the USA. The study showed that subcutaneous semaglutide administered once weekly compared to placebo showed considerable reductions in BMI (16.0% and 5.7%, respectively.) [25]. An observational retrospective study was carried out by Perez-Belmonte *et al.*, among 136 Heart Failure (HF) patients in Spain. The study found that semaglutide demonstrated to be safe, clinically effective, and tolerable among HF patients, improving the overall health and functional status of HF patients from baseline to 12 months [26]. Ryan *et al.* explored the long-term effects of semaglutide on weight loss in 17604 CV patients; and revealed that semaglutide contributed to a major reduction of nearly 20% in the severe adverse events of CV condition among obese patients without diabetes and sustained for 4

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years, and significant weight loss was reported among participants of both sexes, all races and regions [27]. A clinical trial called the Peptide Innovation for Early Diabetes Treatment (PIONEER) program was carried out by Thethi *et al.*, in Germany. The study found that semaglutide taken orally compared to placebo proved to be clinically safe, effective, and tolerable among CVD patients and well-tolerated for glycemic control among T2D patients [28]. A retrospective study consisting of 318 HF Preserved Ejection Fraction (HFpEF) patients (Semaglutide group = 104, placebo group = 214) was conducted by Rehman *et al.*, in Pakistan. This study revealed clinical benefits of semaglutide in HFpEF patients with obesity that it improved CV-related symptoms, physical function, and weight loss [29]. Di Folco *et al.*, (2022) evaluated the impact of semaglutide on cardiovascular risk factors and eating behaviors in patients with type 2 diabetes, reporting significant improvements in glycemic control, weight reduction, and healthier eating patterns, thereby reinforcing semaglutide's role in both metabolic and behavioral aspects of diabetes management [30]. A Semaglutide Treatment Effect in People (STEP) 1 and 4, 68-week controlled trials were conducted by Kosiborod *et al.*, among 1961 and 803 research participants (STEP 1 and 4, respectively) in the USA. The study findings revealed that semaglutide compared to placebo significantly improved cardiometabolic risk factors and reduced anti-hypersensitivity among adults with obesity without diabetes [31]. Rubino *et al.*, (2021), through the STEP 2 randomized clinical trial, demonstrated that weekly subcutaneous semaglutide significantly reduced body weight in adults with overweight or obesity and type 2 diabetes, highlighting its dual benefits in glycemic control and weight management [32].These study findings were similar to an RCT conducted by Jodar *et al.*, in Spain and a comparative review conducted by Klair *et al.*, in the USA [33, 34].A small number of studies conducted with different study designs and approaches for evaluating the safety of semaglutide-based medications with a proper follow-up period for CVH was identified as a limitation of this systematic review. A smaller number of intervention studies evaluate the cost-effectiveness and impact of such interventions or combined with dietary or lifestyle modifications in terms of safety and sustainable weight management was also identified as a limitation of this study. Therefore, continued development of Randomized Control Trials (RCTs), case-control, and prospective studies with a much higher number of overweight participants with CVD or CVH conditions should be conducted with a holistic approach [35].

## CONCLUSIONS

In view of the above, we can conclude that semaglutide is safe and effective for long-term weight loss and improved cardiovascular health among overweight individuals. Consistent positive findings across these varied methodologies and study designs strengthen the conclusion that semaglutide does not merely bring about a significant decrease in weight and body mass index, it also brings about good results for cardiovascular risk factors like blood pressure values or lipid profiles. This evidence directly answers the research question that semaglutide is a valid, sustainable intervention for treating obesity and its associated cardiovascular comorbidities. Nonetheless, more research is needed to better define dosing strategies and the long-term results, to guarantee that semaglutide can be incorporated effectively into more general public health strategies targeting obesity and heart disease.

## Authors Contribution

Conceptualization: MUK
Methodology: SK, MAM
Formal analysis: MNUHK
Writing, review and editing: MUK, HS, DN
All authors have read and agreed to the published version of the manuscript

## Conflicts of Interest

All the authors declare no conflict of interest.

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